REMARKS

Reconsideration of this application is respectfully requested. Claims 1, 36, 38 and 39 have been amended. With these amendments, claims 1, 4-7, 11-15, 18-22, 24-26, 28-30, and 32-39 are currently pending in this application. These amendments are made without prejudice or disclaimer and do not add any new matter. Applicants retain the right to prosecute any cancelled or otherwise unclaimed subject matter in a continuing, divisional or other application as appropriate. Consideration and entry of this reply is respectfully requested.

Claim objections

Claim 36 has been amended to insert SEQ ID numbers. Withdrawal of this objection is therefore respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 36, 38, and 39 stand rejected under 35 U.S.C. § 112, second paragraph, with respect to the term "host". Each of these claims have been amended by replacing the term "host" with the term "mammal". Withdrawal of these rejections is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

A. Rejection of claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 as obvious over Paoletti in view of Emtage, Kirkwood, and Morton

Claims 1, 4-7, 11, 12, 14, 15, 18-23 and 28-34 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Paoletti (U.S. Pat. No. 5,942,235) in view of Emtage (US 2003/0113919), Kirkwood (J. Clin. Oncol. 19(9): 2370-80 (2001)) and Morton et al. ("Morton"; CA Cancer J. Clin. 46(4): 225-44 (1996)). At page 8, the Office Action again refers to the "host" limitation of claims 1, 38 and 39. As explained above, this limitation has been addressed with the amendment of those claims. Claims 38 and 39 have also been amended to include active steps regarding the examination of the mammal of the claims. Claim 1 has also been amended such that step (a) refers to "a mammal having melanoma" which would typically be determined by any of a variety of methods

used by those of skill in the art including, for example, radiology. Applicants respectfully maintain that the rejections in this Office Action are inapplicable to the instantly pending claims.

The Office Action states that "one cannot show nonobviousness by attacking references individually where the rejection is based on a combination of references", citing In re Keller (642 F.2d 413, 208 USPQ 871 (CCPA 1981) and In re Merck & Co. (800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). Applicants understand that "the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, supra, at 425. However, Applicants' approach is very different from the fact patterns of In re Keller and In re Merck. For example, in In re Keller, the expert witness affidavit only addressed the relevance of a single reference from the alleged invalidating combination of references without also addressing the combination. In contrast, the Applicants have addressed each of the cited references individually but also explained how the deficiencies in those individual references renders the combination as a whole ineffective. It is the Applicants' view that this approach is not inconsistent with either In re Keller or In re Merck. It is only after a determination of what each reference may or may not teach has been made that the references may be considered as a combination. Applicants' approach is similar to the manner in which the rejections are presented in the Office Action. The Office Action first pointes out what each reference teaches and then concludes that Applicants' claims obvious). Accordingly, while some of Applicants' remarks initially relate to each reference individually, the deficiencies of the combination of those references as applied to Applicants' claims is subsequently addressed. Thus, Applicants respectfully maintain that their presentation of arguments relating to the cited combinations of references is appropriate and request that the objections to the form in which the same have been presented be withdrawn.

The Office Action begins to explain the rejections by first describing the disclosure of Paoletti. At p. 10, however, the Office Action notes that:

> Paoletti does not explicitly teach (i) a melanoma-associated tumor antigen or IFNα-2b as the sole active pharmaceutical agent recited in claim 1, and gp100 peptides recited in new added claim 36 as the sole active

> pharmaceutical agent, and (ii) subsequently administering at least 10 MU/m^2/day recited in step (b) of claim 1 for cancer vaccine regimen.

Applicants point out that independent claim 1 only relates to the use of "IFNα-2b as the sole active pharmaceutical agent" after step (a) has been completed.

The Office Action then describes the Emtage reference. It is alleged that Emtage teaches the use of "gp100..in diagnosing, treating or preventing melanoma", the use of "compositions of the invention...administered as the sole active pharmaceutical agent", and "kits...for co- or sequential administration."

The Office Action then describes the Kirkwood et al. reference. It is alleged that Kirkwood teaches "high dose IFN-α2b, as the sole active pharmaceutical agent...in the treatment of patients with melanoma." The Office Action notes that:

> Kirkwood et al. do not explicity teach combining high dose IFN-α2b cytokine therapy subsequently to nucleic acid expressing a melanoma-associated antigen as a treatment of melanoma.

At pp. 12-13, the Office Action states that "Morton et al. teaches various combinations of vaccine therapy protocols for treating malignant melanoma...." The Office Action also quotes Morton as shown below:

> Subsequent administration of interferon alfa-2b (IFN alfa-2b) at a dose of $5x10^6$ U/m^2 subcutaneously, three times per week, induced responses in eight of 18 patients who failed Melacine treatment regardless of their HLA phenotype. Based on these results, a national confirmatory phase III trial will compare Melacine plus IFN alfa-2b with IFN alfa-2b alone. This trial will include 300 patients and is scheduled to begin this year[.]"

Applicants note that the instantly claimed methods require administration of "at least 10 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal". As described in Applicants' specification, at least 10 MU/m^2/day IFN-α2b would be understood by one of skill in the art to be a "high-dose" IFN-α2b protocol (e.g., Applicants' paragraph [0072] and Kirkwood et al. J. Clin. Oncol. 18: 2444-2458 (2000)). Applicants' claimed high-dose regimen is understood by those of skill in the art to be very different from a "low-dose" regimen, such as $5x10^6$ U/m^2 as described by Morton. For example, it is know that a high-dose regimen may be associated with complications

from toxicity (e.g., Applicants' paragraph [0083]), which is not observed when using low-dose regimens (e.g., Kirwood, *supra*, p. 2445 ("...given the substantial toxicities associated with high-dose IV IFNa2b, alternative regimens have also been widely investigated."))

At page 13, the Office Action alleges that the combination of these references renders Applicants' pending claims obvious. Regarding Applicants' claims pending as of Sept. 20, 2010, the Office Action at pages 13-14, concludes:

> It is noted that the combination of the teachings by Paoletti regarding the DNA vaccines or compositions can be co-administered or sequentially administered with other anti-neoplastic, anti-tumor or anti-cancer agents and/or with agents which reduce or alleviate ill effects of antineoplastic, anti-tumor or anti-cancer agents; again taking into consideration such factors as the age, sex, weight, and condition of the particular patient, and, the route of administration (See line 55-616, column 13, Paoletti) and the teachings of Morton regarding "Subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of 5×10^6 U/m^2 subcutaneously, three times per week, induced responses in eight of 18 patients who failed Melacine treatment regardless of their HLA phenotype" render the administration of DNA vaccine recited in step (a) of claim 1 and subsequently administering interferon alpha 2b recited in step (b) of claim 1 prima facie obvious.

It is also alleged that Morton's statement that "melanoma patients receiving therapeutic vaccines are usually immunized for prolonged periods" would have provided the motivation "for a skilled artisan to use DNA vaccine taught by Paoletti instead of using the cell lysate of mechanically disrupted melanoma cells lines (Melacine) taught by Morton et al." It is unclear to the Applicants how the fact that "melanoma patients receiving therapeutic vaccines are usually immunized for prolonged periods" would provide "the motivation for a skilled artisan to use DNA vaccine taught by Paoletti instead of using the cell lysate of mechanically disrupted melanoma cells lines (Melacine) taught by Morton et al." Applicants acknowledge that it is known in the art that viral vaccines may be administered "for prolonged periods". However, it is not clear from the Office Action why one of ordinary skill in the art would have been motivated to switch from Paoletti's vaccines to the Melacine composition. The Office Action has not properly explained the basis for this conclusion. And the relevance of this alleged

motivation to change the vaccine compositions to the Applicants' pending claims is not clear; a more complete explanation is therefore respectfully requested.

In another apparent explanation of the basis of rejections, the Office Action concluded at pp. 15-16 that:

> Therefore, it would have been prima facie obvious…to substitute the cytokine (including IFNγ and IL-2) taught by combined teachings of Paoletti and Emtage et al., regarding treating melanoma by administering nucleic acid expressing a melanoma-associated antigen gp100, and subsequently administering a high dose IFN-α2b taught by Kirkwood et al. and Morton et al. and to follow the melanoma vaccination treatment regimens taught by Morton et al. and Kirkwood et al. to arrive at the claimed inventions…*because* i) *Morton et al. specifically teaches* subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x\ 10^6\ U/m^2$ subcutaneously, three times per week, induced responses in 18 melanoma patients who failed Melacine treatment… *and ii) Emtage specifically teaches* peptides, including tumor-associated antigen gp100, nucleic acids encoding such peptides for use in diagnosing, treating, or preventing melanoma, and the compositions can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compositions or agents…. (Emphasis (italics) added).
>
> *It is noted that the Aarts reference was mentioned in the rejection but was previously eliminated as prior art as explained on p. 6 of the Office Action.*

Applicants respectfully maintain that the line of reasoning behind this second "motivation" is also misplaced. The Office Action merely concluded that "[o]ne having ordinary skill in the art would have been motivated to substituted the cytokine (including IFNγ and IL-2) taught by Paoletti" because of what each reference teaches individually. The Office Action has not explained why, for example, one of ordinary skill in the art would move from the non-toxic and apparently successful low-dose regimen of Morton to Applicants' instantly claimed high-dose regimen. No actual motivation or reason that would have driven one of ordinary skill in the art to make the alleged combination has been provided in the Office Action.

At page 22, the Office Action points to KSR International Co. v. Teleflex, Inc. (550 U.S. 398 (2007)) as foreclosing "the argument that a specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness."

Applicants do not disagree with this point. However, both MPEP 706.02(j) and KSR address the initial burden of the USPTO to show "a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references" (there must be "...some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" (KSR, citing In re Kahn, 441 F.3d 977, 988). It is also noted that KSR stated:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See*Graham*, 383 U.S., at 36, 86 S. Ct. 684, 15 L. Ed. 2d 545 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into use of hindsight'" (quoting *Monroe Auto Equip. Co.* v. *Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (CA6 1964))).

And "[w]hile the Court noted that "[r]igid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it", the Federal Circuit has subsequently held that there must be some reason one of ordinary skill in the art would have tried the claimed invention. Rolls-Royce, PLC v. United Technologies Corp. (603 F.3d 1325, 1338 (Fed. Cir. 2010) (attached herewith)) A key issue in that interference case was whether the claimed "forward sweep angle" of a jet engine fan blades was "an easily predictable and achievable variation in view of the disclosure" in the earlier-filed patent, as alleged. *Id.* at 1338. The "forward sweep angle" represented a change in the orientation from that in the earlier-filed patent, but the Federal Circuit found that "[t]he record shows that one of ordinary skill in the art would not reverse the direction of the sweep angle without a clear motivation to do so." *Id.* at 1337. And furthermore:

> Obviousness is a question of law based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the prior art and the claimed invention as perceived before the time of invention; and (4) the extent of any objective indicia of non-obviousness. Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 881 (Fed.Cir.1998). This court reviews a district court's ultimate determination of obviousness without deference, while reviewing the underlying factual inquiries for clear error. Weatherchem Corp. v. J.L. Clark, Inc., 163 F.3d 1326, 1331 (Fed.Cir.1998). If a person of ordinary skill, before the time of invention and without knowledge of that invention, would have found the invention

> merely an easily predictable and achievable variation or combination of the prior art, then the invention likely would have been obvious. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417, 421, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). To preclude hindsight in this analysis, this court flexibly seeks evidence from before the time of the invention in the form of some teaching, suggestion, or even mere motivation (conceivably found within the knowledge of an ordinarily skilled artisan) to make the variation or combination. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1363-65 (Fed.Cir.2008); Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1346-53 (Fed. Cir.2008); Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1355-63 (Fed. Cir. 2007). *Id.* at 1338 (Emphasis added)
>
> ...the record does not show that one of ordinary skill in the art would have any reason to try forward sweep in the outer region at all. A particular course or selection is not obvious to try unless some design need or market pressure or other motivation would suggest to one of ordinary skill to pursue the claimed course or selection. See KSR, 550 U.S. at 421, 127 S.Ct. 1727. In other words, one of ordinary skill must have "good reason to pursue the known options within his or her technical grasp." Id. at 1339. (Emphasis added.)

As explained above, Applicants respectfully maintain that the Office Action has merely concluded that one of ordinary skill in the art would have combined the disclosures of the cited references to produce Applicants' claimed methods. The Office Action not explained why "one of ordinary skill in the art would have any reason to try" (e.g., as in Rolls-Royce) Applicants' claimed method, as legally required. The Office Action merely concluded that, given the content of the individual references, it would have been done. This is clearly an improper hindsight analysis. The cited art simply provided no logical reason to try administering "at least 10 MU/m^2/day as the sole active pharmaceutical agent to the mammal" following administration of "a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent", especially in view of Morton's apparent success with a non-toxic, low-dose regimen. Accordingly, Applicants respectfully maintain that the Office Action has not presented a proper *prima facie* case of obviousness against Applicants' claims. It is therefore respectfully requested that these rejections be withdrawn.

Applicants also disagree with the additional rejection of claims 35 and 37. The Office Action pointed to MPEP 2131.03 and 2144.05 as supporting the allegation that the "absence of repeating step (a) after step (b) recited in claim 35 and step (b) occurs between .5 and 17 months after step (a) recited in claim 37" as merely being "optimization of vaccination and obvious variants of the vaccine regimens taught by combined teachings of Morton et al. (See Figures 2 and 3, pages 231-232, Morton et al.) and Kirkwood et al. (See patients and methods, pages 2371-2372, Kirkwood et al.)." These claimed steps are not merely "optimization" steps but specific time points noted during the development of Applicants' claimed methods that were found to be particularly effective. The Office Action has not explained how these particular time points are disclosed or in some way suggested by the cited art as, for example, "result-effective variables", as required by MPEP § 2131.03(B) (cited on p. 15 of the Office Action). A more complete explanation of these points is therefore respectfully requested. And it is respectfully requested that these rejections be withdrawn.

B. Rejection of claims 24-26 and 36 as obvious over Paoletti in view of Emtage, Kirkwood, Aarts, and Kawakami.

Claims 24-26 and 36 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Paoletti in view of Kirkwood, Emtage, Aarts as described in section (A) above, and further in view of Kawakami (U.S. Pat. No. 5,844,075). Applicants respectfully maintain that these references cannot be combined to support a *prima facie* case of obviousness against the instantly pending claims.

Applicants' position with respect to the combination of Paoletti, Kirkwood, Emtage, and Morton disclosures were set forth in the preceding section, and are maintained with respect to these rejections. The Office Action alleges that Kawakami teaches gp100 peptides but does not suggest that the reference can substitute for Morton's alleged teaching of vaccine/cytokine combination therapies. Accordingly, the reference cannot be used in combination with Paoletti, Kirkwood, and Emtage to support a proper *prima facie* case of obviousness regarding the instantly pending claims. It is therefore respectfully requested that these rejections be withdrawn.

CONCLUSIONS

Reconsideration of this application is respectfully requested. Applicants believe the claims are in condition for allowance and respectfully request the issuance of a Notice of Allowance as soon as possible. The Examiner is encouraged to contact the undersigned if it is believe doing so would expedite prosecution of this application.

Respectfully submitted,

Date: June 14, 2011

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